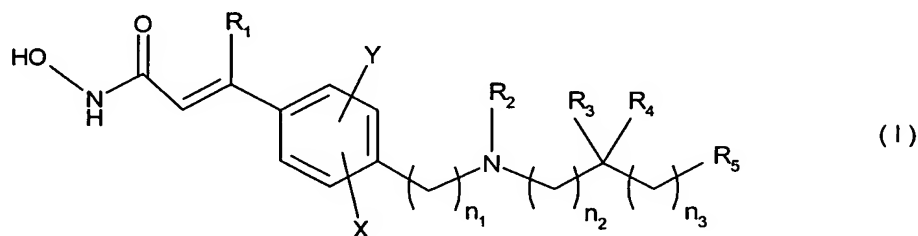


Amendments to the Claims:

Listing of the Claims:

Cancel Claims 1-15.

Claim 16 (original): A method of treating, preventing or suppressing an immune disorder, immune response or immune mediated response of an animal comprising administering to said animal an effective amount of an histone deacetylase inhibitor compound of formula I:



wherein

R_1 is H, halo, or a straight chain C_1 - C_6 alkyl;

R_2 is selected from H, C_1 - C_{10} alkyl, C_4 - C_9 cycloalkyl, C_4 - C_9 heterocycloalkyl, C_4 - C_9 heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, $-(CH_2)_nOC(O)R_6$, amino acyl, $HON-C(O)-CH=C(R_1)$ -aryl-alkyl- and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently H, C_1 - C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound represent $C=O$, $C=S$, or $C=NR_8$, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound can form a C_4 - C_9 heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1 - C_6 alkyl, C_4 - C_9 cycloalkyl, C_4 - C_9 heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, and mixed aryl and non-aryl polyheterocycle;

n , n_1 , n_2 and n_3 are the same or different and independently selected from 0 - 6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4 ;

X and Y are the same or different and independently selected from H, halo, C₁-C₄ alkyl, NO₂, C(O)R₁, OR₉, SR₉, CN, and NR₁₀R₁₁;

R₆ is selected from H, C₁-C₆ alkyl, C₄ - C₉ cycloalkyl, C₄ - C₉ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR₁₂, and NR₁₃R₁₄;

R₇ is selected from OR₁₅, SR₁₅, S(O)R₁₆, SO₂R₁₇, NR₁₃R₁₄, and NR₁₂SO₂R₆;

R₈ is selected from H, OR₁₅, NR₁₃R₁₄, C₁-C₆ alkyl, C₄ - C₉ cycloalkyl, C₄ - C₉ heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R₉ is selected from C₁ - C₄ alkyl and C(O)-alkyl;

R₁₀ and R₁₁ are the same or different and independently selected from H, C₁-C₄ alkyl, and -C(O)-alkyl;

R₁₂ is selected from H, C₁-C₆ alkyl, C₄ - C₉ cycloalkyl, C₄ - C₉ heterocycloalkyl, C₄ - C₉ heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl, and heteroarylalkyl;

R₁₃ and R₁₄ are the same or different and independently selected from H, C₁-C₆ alkyl, C₄ - C₉ cycloalkyl, C₄ - C₉ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, amino acyl, or R₁₃ and R₁₄ together with the nitrogen to which they are bound are C₄ - C₉ heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R₁₅ is selected from H, C₁-C₆ alkyl, C₄ - C₉ cycloalkyl, C₄ - C₉ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and (CH₂)_mZR₁₂;

R₁₆ is selected from C₁-C₆ alkyl, C₄ - C₉ cycloalkyl, C₄ - C₉ heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and (CH₂)_mZR₁₂;

R₁₇ is selected from C₁-C₆ alkyl, C₄ - C₉ cycloalkyl, C₄ - C₉ heterocycloalkyl, aryl, aromatic polycycle, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and NR₁₃R₁₄;

m is an integer selected from 0 to 6; and

Z is selected from O, NR₁₃, S and S(O);

or a pharmaceutically acceptable salt thereof.

Claim 17 (original): A method for preventing or treating acute or chronic transplant rejection in a recipient patient of organ or tissue or cell transplant comprising the step of administering to said patient a therapeutically effective amount of a compound of formula (I) according to claim 16.

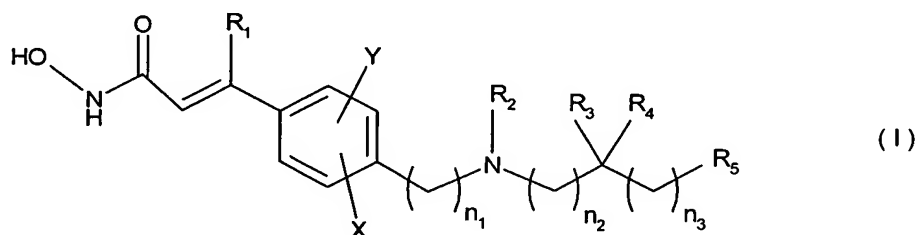
Claim 18 (currently amended): A method according to claim 16 or 17 further comprising a second pharmacologically active agent.

Claim 19 (original): A method according to claim 18 wherein the second pharmacologically active agent is selected from immunosuppressive agents, immunomodulating agents, antibiotics, antiviral agents, steroids, NSAIDS or mixtures thereof.

Claim 20 (currently amended): A method for enhancing graft survival following transplant, comprising administering to an animal previous to, concurrently with, or subsequent to a transplant procedure an effective amount of an histone deacetylase inhibitor compound of formula I according to claim 1516.

Claim 21 (new): A combination for use in the treatment, prevention or suppression of an immune disorder, immune response or immune mediated response, or for the prevention or treatment of acute or chronic transplant rejection in a recipient patient of an organ, tissue or cell transplant, which comprises (a) a histone deacetylase inhibitor and (b) a second pharmacologically active agent in which (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt or a pharmaceutically acceptable prodrug thereof, for simultaneous, concurrent, separate or sequential use.

Claim 22 (new) The combination according to Claim 21 wherein the histone deacetylase inhibitor is a compound of formula (I):



wherein

R₁ is H, halo, or a straight chain C₁-C₆ alkyl;

R₂ is selected from H, C₁-C₁₀ alkyl, C₄ - C₉ cycloalkyl, C₄ - C₉ heterocycloalkyl, C₄ - C₉ heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, -(CH₂)_nC(O)R₆, -(CH₂)_nOC(O)R₆, amino acyl, HON-C(O)-CH=C(R₁)-aryl-alkyl- and -(CH₂)_nR₇;

R₃ and R₄ are the same or different and independently H, C₁-C₆ alkyl, acyl or acylamino, or R₃ and R₄ together with the carbon to which they are bound represent C=O, C=S, or C=NR₈, or R₂ together with the nitrogen to which it is bound and R₃ together with

the carbon to which it is bound can form a C₄ – C₉ heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R₅ is selected from H, C₁-C₆ alkyl, C₄ – C₉ cycloalkyl, C₄ – C₉ heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, and mixed aryl and non-aryl polyheterocycle;

n, n₁, n₂ and n₃ are the same or different and independently selected from 0 – 6, when n₁ is 1-6, each carbon atom can be optionally and independently substituted with R₃ and/or R₄;

X and Y are the same or different and independently selected from H, halo, C₁-C₄ alkyl, NO₂, C(O)R₁, OR₉, SR₉, CN, and NR₁₀R₁₁;

R₆ is selected from H, C₁-C₆ alkyl, C₄ – C₉ cycloalkyl, C₄ – C₉ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR₁₂, and NR₁₃R₁₄;

R₇ is selected from OR₁₅, SR₁₅, S(O)R₁₆, SO₂R₁₇, NR₁₃R₁₄, and NR₁₂SO₂R₆;

R₈ is selected from H, OR₁₅, NR₁₃R₁₄, C₁-C₆ alkyl, C₄ – C₉ cycloalkyl, C₄ – C₉ heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R₉ is selected from C₁ – C₄ alkyl and C(O)-alkyl;

R₁₀ and R₁₁ are the same or different and independently selected from H, C₁-C₄ alkyl, and -C(O)-alkyl;

R₁₂ is selected from H, C₁-C₆ alkyl, C₄ – C₉ cycloalkyl, C₄ – C₉ heterocycloalkyl, C₄ – C₉ heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl, and heteroarylalkyl;

R₁₃ and R₁₄ are the same or different and independently selected from H, C₁-C₆ alkyl, C₄ – C₉ cycloalkyl, C₄ – C₉ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, amino acyl, or R₁₃ and R₁₄ together with the nitrogen to which they are bound are C₄ – C₉ heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R₁₅ is selected from H, C₁-C₆ alkyl, C₄ – C₉ cycloalkyl, C₄ – C₉ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and (CH₂)_mZR₁₂;

R₁₆ is selected from C₁-C₆ alkyl, C₄ – C₉ cycloalkyl, C₄ – C₉ heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and (CH₂)_mZR₁₂;

R₁₇ is selected from C₁-C₆ alkyl, C₄ – C₉ cycloalkyl, C₄ – C₉ heterocycloalkyl, aryl, aromatic polycycle, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and NR₁₃R₁₄;

m is an integer selected from 0 to 6; and

Z is selected from O, NR₁₃, S and S(O);

or a pharmaceutically acceptable salt thereof.

Claim 23 (new): The combination of claim 21 wherein the second pharmacologically active agent is selected from immunosuppressive agents, immunomodulating agents, steroids, NSAIDS or mixtures thereof.

Claim 24 (new): The combination of claim 21 wherein the second pharmacologically active agent is selected from sphingosine 1-phosphate receptor agonist, e.g. FTY-720 or an analog thereof, mTOR inhibitors, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin; calcineurin inhibitors, cyclosporine, CCI779, ABT578, a rapalog or AP23573, AP23464, AP23675 or AP23841; TAFA93, biolimus-7, biolimus-9, an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; cyclophosphamide; methotrexate; a somatostatin analogue like octreotide, lanreotide, vapreotide or SOM230; a deoxyspergualine compound or derivative or analog thereof, e.g. 15-DSG, monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD11a/CD18, CD25, CD27, CD28, CD40, CD45, CD58, CD80, CD86, CD134, CD137, ICOS, CD150 (SLAM), CD152, OX40, 4-1BB or to their ligands, e.g. CD154, or antagonists thereof; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4lg (for ex. designated ATCC 68629) or a homologue or a mutant thereof, e.g. LEA29Y; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, anti-LFA-1 or anti-ICAM antibodies, VCAM-4 antagonists or VLA-4 antagonists; or anti-chemokine antibodies or anti-chemokine receptor antibodies or low molecular weight chemokine receptor antagonists, e.g. anti MCP-1 antibodies, and mixtures thereof.

Claim 25 (new): The combination of claim 21 wherein the histone deacetylase inhibitor is selected from the group consisting of N-hydroxy-3-[4-[[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide and N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable prodrug thereof.

Claim 26 (new): A combination according to 21 wherein the HDAC compound and the second pharmaceutically active agent are present synergistically effective amounts.

Claim 27 (new): A combination according to 21 wherein the HDAl compound inhibitor has an IC₅₀ of <500 nM in the mouse or human mixed lymphocyte reaction (MLR).

Claim 28 (new): A method of treating, preventing or suppressing an immune disorder, immune response or immune mediated response of an animal comprising administering to said animal an effective amount of an histone deacetylase inhibitor having an IC₅₀ of <500 nM in the mouse or human mixed lymphocyte reaction (MLR).